

Remarks

I. Status of the Claims

Claims 3-8, 12-16 and 19 are currently pending.

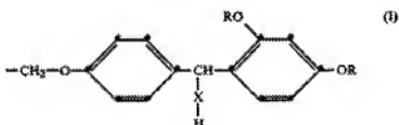
The withdrawal of the previous grounds of rejection under 35 USC 112 second paragraph, 35 USC 102(b) based on each of Birr and Merrifield as evidenced by Finger is noted with appreciation.

The withdrawal of claim 15 from consideration is respectfully traversed, as discussed in greater detail below.

II. Response to Claim Rejection, §103(a) – Rink, Mihala, Merrifield, and Finger

The rejection of claims 3-8, 12-14, 16 and 19 as obvious under this combination of references is respectfully traversed.

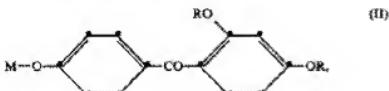
Rink (U.S. 5,004,781) discloses a resin suitable for use in a Merrifield solid-state peptide synthesis, a method for making the resin, and a method of using the resin in solid state peptide synthesis. The resin of Rink is characterized (col. 1, lines 16-28) in that it has been substituted at benzene rings of its skeletal structure by groups of the formula



in which X represents -O- or -NH- and R represents C₁-C₄ alkyl.

The method of making the resin is discussed at col. 3, line 6 – col. 5, line 25. In the method of making the resin, a suitable polystyrene is reacted, in succession,

(a) with a compound of formula



in which M is an alkali metal and R has the meaning given above.

- (b) with a reducing agent and, if X represents —NH—,
- (c) with a reagent that introduces the amino group.

(Rink, col. 3, lines 36-53) In process step (b) of Rink, the oxo group of formula II is converted to a hydroxyl group (col. 4, lines 10-13). If “X” in formula (I) is to be an —NH-, then the hydroxyl group is converted to an amino group to convert the “hydroxyl resin” to the “amino resin” (col. 4, lines 32-35). The source of the amino groups can be ammonia gas (col. 4, lines 35-42) or carbamates (col. 4, lines 43-47). “In this manner a synthetic resin of the above-defined structure is obtained that carries instead of the —X-H group a —NH-W group in which W represents an amino-protecting group ...” (col. 5, lines 2-5) To free the “amino resin” to provide a binding site for subsequent use in peptide synthesis, the amino-protecting group W is removed with a base such as a tertiary or secondary amine (col. 5, lines 7-12), or with “...an alkali metal hydroxide, for example sodium hydroxide, or an ammonium hydroxide, for example benzyltrimethylammonium hydroxide...” (col. 5, lines 19-22).

It may be seen that this portion of Rink relates to a method of making a support resin, **not** to a procedure for conducting a Merrifield solid-state peptide synthesis.

Use of the “hydroxyl resin” as a support for a peptide synthesis is discussed at col. 5, line 48 – col. 8, line 5. Use of the “amino resin” as a support for a peptide synthesis is discussed beginning at col. 8, line 6. To synthesize the peptide, the amino resin is reacted with a protected amino acid or protected amino acid sequence, for example a compound of the formula $W^1 - AM^1 - OH$ in which W^1 represents an N-terminal amino protecting group and AM^1 represents the acyl radical of an amino acid sequence. “This results in a resin with an attached C-terminal amide, that is to say a resin in which the benzene rings have been substituted by radicals of Formula III.” (col. 8, lines 13-16) In other words, the C-terminal amide of Formula III attached to the

amino resin serves as the starting point for peptide synthesis. The peptide is then synthesized and detached from the resin as described in connection with the hydroxyl resin.

Note that Rink uses “W” to denote the amino-protecting group on the *resin*, and “W¹” and “W²” to denote the amino-protecting groups on the synthesized *peptide* that is built on the resin backbone, then detached.

The selection of the N-terminal amino-protecting groups W¹ and W² for use in synthesizing the peptides, and the effect of that selection on the ease of detachment of the peptide from the resin, is discussed at col. 8, lines 24-51. In order to synthesize the peptide, it is necessary to remove the amino-protecting group W¹ or W² from the *peptide* without detaching the peptide from the *resin*. In some embodiments, W¹ and W² can be Fmoc (col. 8, line 42). Rink states that during the peptide synthesis, the groups W¹ and W²

“can be removed with inorganic or organic bases, especially with tertiary or secondary amines, such as those mentioned hereinbefore for the manufacture of the ‘amino resin.’ The conditions for the removal of the N-terminal amino-protecting group in accordance with process step (b) [i.e., removal of the protecting group from the peptide to allow attachment of another amino acid residue], especially of the Fmoc group, are described hereinabove in connection with the manufacture of the ‘amino resin’ and are generally known.” (col. 8, lines 43-51, emphasis added).

Thus, Rink teaches that, of the bases taught at col. 5 lines 7-25, the preferred bases for removing the N-terminal amino protecting group from the peptide is a *tertiary or secondary amine*, not a *quaternary amine*. This is significant in view of Rink’s teachings that the factors that determine the choice of a base for removal of a protecting group during peptide synthesis are different from the factors that determine the choice of a base for removal of a protecting group during resin manufacture, because during peptide synthesis care must be taken to choose a base that does not cause detachment of the peptide from the resin. This is not a factor during resin manufacture. Thus Rink teaches *away* from the use of the quaternary amine salts recited in the present claims, by teaching that it is not a preferred means for removing the amino protecting group during peptide synthesis.

In citing to Rink, the Action conflates the procedures for removal of protecting groups during *resin manufacture* and during *peptide synthesis*, by referencing these different portions of the reference together. See, page 4, lines 7, 16-17, 18-19; p. 6, lines 13-14; page 7, line 8; page 8,

line 7; page 9, lines 16-17; page 10, line 21; page 11, line 22 – page 12, line 1. Yet the reference is clear that removal of a protecting group W¹ or W² from the *peptide* presents different issues than removal of a protecting group W from the *resin*, as shown by the fact that Rink teaches that bases that are suitable for protecting group removal from the resin are not among those that are preferred for protecting group removal from the peptide. In fact, Rink’s teaching that use of benzyltrimethylammonium hydroxide allows for the use of lower temperatures and shorter reaction times during resin manufacture suggests that it is a stronger base than the tertiary and secondary amines preferred during peptide synthesis, from which one skilled in the art might conclude that it might in fact be too strong for use in peptide synthesis, and possibly could cause premature detachment of the peptide from the resin or other undesirable reactions.

And, as the Action correctly points out, Rink does not teach the use of benzyltrimethylammonium hydroxide at any and all of the process steps, nor does Rink teach its use in any of the examples, further demonstrating that it is not a preferred choice, such that one skilled in the art upon reading Rink would not choose to use it during peptide synthesis.

Mihala teaches a solid phase peptide fragment condensation protocol in which the coupling step (step c of representative claim 3 herein) is conducted in a 3:1 chloroform-phenol solvent system with a combination of 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt) and its tetrabutylammonium (TBA) salt as additive. (Abstract) Specifically, Mihala found that using HODhbt coupled to the TBA salt in 3:1 chloroform-phenol solvent worked better than using HODhbt alone in DMF solvent. (*Id.*) The TBA*ODhbt salt of Mihala is not one of the salts recited in claim 3, and Mihala does not suggest that any other salts are interchangeable with TBA. Moreover, claim 3 specifically recites that if the salt is added in step c, then the solvent system is *not* to be chloroform-phenol. Mihala therefore teaches **away** from the invention as presently claimed, because Mihala teaches that the best results are achieved by use of a salt that is not claimed and the use of a solvent that is specifically excluded by the claims.

As the Action notes (page 10, lines 1-3), Mihala at page 565 first column recites that the “art recognizes a wide variety of solvents including DMF, NMP, DMSO, TFE-DCM...” But Mihala notes at page 565 that fully protected Boc-peptides are insoluble in DMF, NMP, and DMSO. Thus Applicants respectfully traverse the Action’s statement that “Mihala does not discredit the use of any particular solvent system.” (Action, page 10, line 5) One skilled in the

art would not have been motivated to look to such other solvent systems, where Mihala taught that such other systems would not dissolve fully protected Boc-peptides and instead focused exclusively on the 3:1 chloroform/phenol solvent specifically excluded from the present claims.

Even if Rink and Mihala taken together are interpreted to teach peptide synthesis and the use of ammonium salts during the process, that does not render the present invention obvious, where the present invention is directed to the use of particular quaternary salts and excludes the solvent system embraced by Mihala. Merrifield does not make up for these deficiencies, for the reasons noted in the prior response. In particular, Merrifield does not teach a procedure in which the peptides attached to a resin support are provided with an α -amino protecting group which is then removed before another amino acid is added, as recited in the preamble and step a) of the present claims. Accordingly, there would be no reason for one skilled in the art to choose the particular salt used in Merrifield over all the various salts available in the art, nor is there any reason why one skilled in the art would believe that such a selection would work.

The Action states at page 6, lines 1-2, "Importantly Merrifield teach that the presence of triton B enabled a particular reaction to occur (abstract)." It is believed that the Action is referring to the reaction described in Merrifield at page 1293, second column, under "Acylation" The second paragraph under that sub-heading states,

"When a strong base such as Triton B was used to deprotonate the amidinopeptide resins, acylation became possible with a DCC-activated Boc-amino acid or with a preformed symmetrical anhydride. Thus HCl-Dca-Gly-Val-Res gave 63% of Ala-Dca-Gly-Val-Res."

Dca is dicyclohexylamidino (Merrifield, Abstract). This group is not an amino acid. The fact that Triton B deprotonated this group to allow acylation does not necessarily mean that Triton B would facilitate peptide synthesis in the method as recited in the present claims, which requires cleaving an α -amino protecting group, washing, then adding an α -amino protecting group.

With regard to the comments on page 8 of the Action, Applicants acknowledge that the solid phase peptide synthesis technique is known in the art. What is new and non-obvious is the particular steps and additives as recited in the present claims. The teaching of other ammonium salts at various stages of the process does not render obvious the use of any of benzyltrimethylammonium hydroxide, benzyltrimethylammonium chloride,

benzyltrimethylammonium carbonate, tetrabutylphosphonium bromide and triethylsulfonium tetrafluoroborate as recited in the present claims. Rink's teaching of the use of benzyltrimethylammonium hydroxide to remove an amino protecting group in a *resin* synthesis does not render obvious the use of such a strong base in a *peptide* synthesis, especially where the reference itself suggests the use of milder bases for that purpose. Merrifield's teaching of benzyltrimethylammonium hydroxide in a reaction is not pertinent herein because Merrifield does not teach a procedure in which the peptides attached to a resin support are provided with an α -amino protecting group which is then removed before another amino acid is added, as recited in the present claims. With regard to Mihala's teachings of the use of the benefits of the tetrabutyl ammonium salts, the Action provides no basis for extrapolating those teachings to the use of the claimed salts, particularly where Mihala teaches the use of a solvent system expressly excluded from the present claims.

Therefore, in view of the foregoing and in light of the clarifying amendments to the claims presented herein, Applicants believe that this rejection has been overcome.

III. Rejoinder of Claim 15

In the Office Action of July 24, 2008, the Office required elections of species with respect to the salt and the alpha amino protecting group. The action stated, "Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of the allowed generic claim as provided by 37 CFR 1.141." In the present case, all of the independent claims have been shown to be allowable over the cited art of record. Previously withdrawn claim 15, which depends from allowable claim 3 and includes all the limitations thereof, is now entitled to consideration, as stated in the original Action. It is respectfully requested that claim 15 be rejoined in the case.

Conclusion

Applicants submit that the rejections proffered by the Office have been overcome, and that the Application is now in condition for allowance. The Applicants invite the Examiner to contact the undersigned as indicated below if the Examiner believes that this would expedite prosecution of this application.

Respectfully submitted,

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